## REMARKS

Claims 1-8, 11-14 and new claims 15-17 are pending. The support in the originally filed specification for the amendments and new claims is as follows: Claims 5-8 are amended with the subject matter of claims 1 and 10; Claim 15: p.12, lines 20-37; Claim 16: p.17, lines 20-28 and Claim 17: p.13, lines 1-7. No new matter is added.

**Claims 5 - 10 are objected to because of the following informalities: claims 5 - 10 depend from withdrawn claim 1.** (Office Action, page 2)

Claims 5-8 are rewritten in independent form and claims 9-10 are canceled making this objection now moot.

**Claims 5 - 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rossi et al. (Curr Eye Res, 1990) in view of Brodnitz et al. (J Agr Food Chem, 1971).** (Office Action, page 3)

Rossi et al. reports the effect of eledoisin on lacrimal secretion. It was shown that eledoisin causes lacrimal gland secretion to increase though an irritative sensory reflex mechanism (see ABSTRACT and the last paragraph of DISCUSSION). In the experiments they employed, eledoisin was topically applied to the eye of rabbit (i.e. application in a contact manner). In summary, Rossi et al. only shows the effect of eledoisin on lacrimal secretion when it was applied **in a contact manner**. Eledoisin was applied directly to the eye of rabbit for the purpose of examining its possible application as a treatment for dry eye. Their experiments are not enough to exclude the effect of stimulation by a direct contact with experiment instruments or materials stimulates, which generated reflex lacrimal secretion, because, in their experiments, the excretory duct cannula was connected to drain (see page 274, left column, lines 5 to 7) or sponges were used to collect fluid at inferior eyelid (see page 274, left column, lines 35 to 39) for evaluation of tear volume.

In contrast, the instant invention as claimed is a method of lacrimation examination comprising a step in which the specific reagent is exposed to an eye **in a non-contact manner**, as further specifically recited in new Claims 15-17. The lachrymatory factor is volatile and thus it stimulates eyes in a non-contact manner. The claimed invention is decisively different from the method of Rossi et al. as to a manner of contact in addition to the chemicals used. Therefore,

even though the chemical, which is used as an active ingredient of the reagent, is known as disclosed in Brodnitz et al., the claimed invention is not obvious from the combination of Rossi et al. and Brodnitz et al.

Rossi et al., merely reports that lacrimal secretion was observed when the chemical (i.e. eledoisin) was applied to the eye of rabbit. No teaching or suggestion as to applicability of the chemical to lacrimation examination for human is found in Rossi et al. Turning to Brodnitz et al., it merely reports that thiopropanal S-oxide was successfully identified as the lachrymatory factor in onion with the results of analysis on properties. No description concerning a specific use of thiopropanal S-oxide is found in Brodnitz et al. Combination of the teaching of Brodnitz with Rossi et al. does not cure the deficiencies of Rossi.

In addition to the fact that the combination of the references fails to create a prima facie teaching of obviousness, the following facts support a conclusion of non-obviousness of the instant invention. The present inventors successfully made the instant inventions based in part on the following findings (1) to (6):

(1) By using the lachrymatory component in onion, the tear volume increased within a short time and the change in the tear volume was transient. This result suggests that the lacrimatory component is effective as a stimulant of lacrimation and that the use thereof does not produce any adverse side effects. Further, this result means that when the lacrimatory component is used for lacrimation examination, measurement can be completed in a short time.

(2) When one of the eyes of a subject was exposed to the lacrimatory component, lacrimation was induced in the other eye that was not exposed (non-exposed eye). This means that the lacrimatory component exerts an extremely high lacrimation effect.

(3) Difference in time taken before the stimulation of the lacrimatory component was felt and in the degree of stimulation felt by the subject was found between normal subjects and dry eye patients. Therefore, it is suggested that the stimulation of the lacrimatory component can be used as an index in diagnosis of dry eye.

(4) Difference in the dynamics of the lacrimation by the stimulation of the lacrimatory component was found between normal subjects and dry eye patients. Furthermore, difference in the dynamics of the lacrimation was found between a slight/moderate group of dry eye patients and a severe group of dry eye patients. These findings mean that the use of the amount of

lacrimation induced by the stimulation of the lacrimatory component as an index allows not only diagnosis of dry eye but also the determination of the severity of dry eye conditions.

(5) In both normal subjects and dry eye patients, the tear volume returned to the initial volume within a short time after the stimulation of the lacrimatory component had been given. Thus, it is suggested that, not only in normal subjects, but also in dry eye patients, the effect of the lacrimatory component is transient and that the adverse effects to the ocular surface does not occur.

(6) Although the average degree of stimulation from the lacrimatory component reported by each subject was different between normal subjects and dry eye patients, both returned to zero (i.e., no stimulation) at the end of the examination, and no effect on the epithelium of the ocular surface was observed after the examination. These results indicate that there are no substantial adverse effects by the stimulation of the lacrimatory component on the ocular surface. Therefore, when the lacrimatory component is used as a reagent for examining dry eye, there is little chance for any side effects (adverse effects) to occur, and that the lacrimatory component can be used repeatedly for an extended time.

The present inventors showed more specifically that the lachrymatory factor makes it possible to provide a superior examination method to evaluate ocular-surface sensation and lacrimal gland function (see "Jpn J Ophthalmol 2010; 54: 215-220", a copy of which is enclosed).

As is apparent from the above, the instant invention was never made without the inventors' accomplishment that the actual effectiveness of the lacrimatory component in onion, to which the instant inventors noted, was revealed by experiments. In particular, the fact that the tear volume increased within a short time and the change in the tear volume was transient when the lacrimatory component was used and that the lacrimatory component did not produce any adverse side effects are essential and very important characteristics for a reagent used for lacrimation examination. In addition, the effectiveness of the lacrimatory component was supported by the fact that the lacrimation was promoted also in dry eye patients by stimulation of the lacrimatory component and that no effect on the epithelium of the ocular surface was observed.

A chemical to be used as a reagent for lacrimation examination should have a lacrimation effect. However, this feature by itself does not allow determination of actual efficacy of the

chemical. Namely, not all of the chemicals that exert a lacrimation effect can be applied to lacrimation examination.

Rossi et al. as well as Brodnitz et al. only teach that the chemical they used showed a lacrimation effect. Neither of these papers provides any teachings nor suggestions, which are supported by the experimental data, as to applicability of these chemicals as a reagent for lacrimation examination.

The combination of Rossi et al. and Brodnitz et al cannot create a *prima facie* conclusion of obvious of the invention now claimed. It is respectfully requested that the rejection be reconsidered and withdrawn.

**Claims 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rossi et al. and Brodnitz et al. as applied to claims 5 - 8 above, and further in view of Yokoi et al. (Br J Ophthalmol, 1999).** (Office Action, page 5)

Claims 9 and 10 are canceled making this rejection moot.

In view of the above amendment, applicant believes the pending application, including new claims 15-17, is in condition for allowance.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

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Respectfully submitted,

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Encls: Jpn J Ophthalmol 2010; 54: 215-220